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Recent Developments in the Catalytic, Asymmetric Construction of Pyrroloindolines Bearing All-Carbon Quaternary Stereocenters

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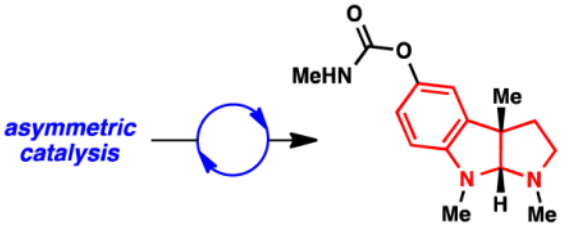
Abstract



Pyrroloindoline alkaloids constitute a large family of natural products that has inspired the development of an impressive array of new reactions to prepare the key heterocyclic motif. This synopsis will address catalytic, asymmetric reactions developed to synthesize pyrroloindolines bearing C3a all-carbon quaternary stereocenters. The methods described herein include both transition metal-catalyzed and organocatalyzed reactions that have been demonstrated suitable for the synthesis of the pyrroloindoline framework.

The hexahydropyrrolo[2,3-*b*]indole, commonly referred to as the pyrroloindoline, is a common heterocyclic motif that unites several structurally diverse and biosynthetically distinct families of alkaloids (Figure 1, highlighted in red).[1] Alkaloids possessing the pyrroloindoline framework exhibit a broad array of biological properties, ranging from antibacterial[2] and anticancer activities[3] to the inhibition of cholinesterase.[4] Many pyrroloindoline natural products bear C3a all-carbon quaternary stereocenters, and the synthetic challenge inherent to these structures, combined with their promising medicinal value, has inspired the development of a variety of inventive methods for the enantioselective preparation of the core heterocycle.[5] Although numerous strategies involving either chiral auxiliaries or the functionalization of L-tryptophan have been developed, this synopsis will focus on the catalytic, enantioselective approaches based on the recent growth of research within this field.

Catalytic, asymmetric reactions to prepare pyrroloindolines can be categorized primarily into two general approaches: (1) reactions to synthesize 3,3′-disubstituted oxindoles, which can be elaborated to the corresponding pyrroloindolines,[6] or (2) tandem C3-functionalization/cyclization reactions of 3-substituted indoles. Extensive research has been conducted using both approaches, and each possesses distinct advantages. The indole

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functionalization approach permits direct access to pyrroloindolines, whereas the oxindoles can serve as intermediates in the synthesis of both pyrroloindoline and oxindole-based natural products.

Pyrroloindoline Synthesis via 3,3-Disubstituted Oxindoles

3,3′-Disubstituted oxindoles are available by several methods including α-alkylation, intramolecular cyclization, and intramolecular acyl migration. The first catalytic asymmetric synthesis of a 3,3′-disubstituted oxindole was developed in 1991 at Hoechst-Roussel Pharmaceuticals Inc.[7] Researchers Wong and Lee discovered that subjection of oxindole **6** to chloroacetonitrile in the presence of cinchoninium bromide catalyst **7** delivered enantioenriched oxindole **8** (Scheme 1). Further elaboration resulted in a formal total synthesis of the anticholinesterase natural product physostigmine (**1**, Figure 1). This approach built on the pioneering phase transfer catalysis studies of Dolling and coworkers,[8] and has been succeeded by several enantioselective organocatalytic α-alkylation reactions of oxindoles.[9] Recently, Luo and coworkers identified a bifunctional tertiary amine thiourea (**10**) that catalyzes the conjugate addition of 3-aryl and 3-alkyloxindoles (**9**) to 2-chloroacrylonitrile (**11**).[9c] Of the asymmetric oxindole alkylation approaches reported to date, this is the first method that directly installs an appropriate C2-handle for advancement to diketopiperazine-based alkaloids (e.g. chaetocin A (**3**), Figure 1).

A second, foundational catalytic asymmetric method to prepare 3,3-disubstituted oxindoles was the Pd-catalyzed intramolecular Heck reaction reported by Overman and coworkers in 1993 (Scheme 2).[10] In a preliminary demonstration of the synthetic utility, physostigmine (**1**, Figure 1) was prepared from *Z*-butenanilide **14** via oxindole carboxaldehyde **15**. Recently, this reaction was applied in more elaborate contexts including the synthesis of the alkaloids minfiensine (**4**, Figure 1)[11] and polypyrroloindoline quadrigemine C.[12] These transformations are noteworthy examples of asymmetric Heck reactions that generate all-carbon quaternary centers, and have likely inspired the development of related transition metal-catalyzed cyclization reactions for the construction of pyrroloindolines.[13] For example, Nakao, Hiyama, Ogoshi and coworkers reported the synthesis of (2-oxindolyl)acetonitrile derivatives (e.g. **8**) by the Ni-catalyzed enantioselective intramolecular arylcyanation of alkenes (Scheme 2).[13c,14] A key finding in this study was that, in addition to the nickel catalyst, a Lewis acid ($AlMe_2Cl$) was required to promote oxidative addition of the arylnitrile. Subsequent C-H oxidation furnishes the highly enantioenriched 3,3′-dialkyl (**8**) and 3-alkyl-3′-aryloxindoles.

In addition to the Heck-type cyclization reactions described above, transition metal-catalyzed asymmetric allylic alkylation (AAA) reactions to prepare 3,3-disubstituted oxindoles have been developed. In 2006, Trost and Zhang reported the Mo-catalyzed AAA of oxindoles using allyl carbonates as electrophiles,[15] and established that these products could be easily elaborated to the corresponding pyrroloindolines. More recently, the same group developed a Pd-catalyzed AAA reaction of oxindoles using benzyloxyallene **19** as the electrophile (Scheme 3).[16,17,] The advantages of the latter reaction are that (1) it tolerates 3-indolyloxindole substrate **18**, and (2) the benzyloxy substituent in oxindole **21** provides a useful handle for the synthesis of more oxidized pyrroloindoline frameworks, such as that found in gliocladin C and related natural products (**2**, Figure 1).

Most oxindole α-alkylation strategies harness the intrinsic nucleophilicity of enolate intermediates; however, two recent umpolung approaches employ oxindoles as the electrophilic component.[18] In a 2009 report, Stoltz and coworkers describe a Cu(II) bisoxazoline (**23**)-catalyzed stereoablative alkylation of 3-chloro-3-aryloxindoles (**22**) with dimethylmalonate, wherein coordination of the malonate to the copper catalyst presumably

generates a chiral nucleophile (**24**, Scheme 4).[18a] The reaction is proposed to occur by elimination of HCl from **22** to form a transient *o*-azaxylylene (**25**); subsequent attack at C3 by **24** delivers the 3,3′-disubstituted oxindole (**26**). The utility of these products in pyrroloindoline synthesis was demonstrated for oxindole **26**, which following Krapcho dealkoxycarbonylation, *N*-methylation, aminolysis, and reductive cyclization afforded 3-phenylpyrroloindoline **28** in an operationally straightforward manner.

Gong and coworkers have discovered an alternative strategy for the in situ generation of electrophilic oxindole species that has proven instrumental for bispyrroloindoline synthesis.[18b] This reaction involves indole-assisted dehydration, followed by chiral phosphoric acid (**31**)-catalyzed addition of enamine **30** to the transient azafulvene (Scheme 5). Mechanistic insight was provided by DFT calculations, which suggest a two-point binding model for the Brønsted acid that invokes hydrogen bonding of both the enamine and indole nitrogens (see proposed transition structure **32**). The necessary nitrogen functionality was installed by a Beckmann rearrangement to give **34**, which was elaborated in eight additional steps to (+)-folicanthine (**35**). Gong and coworkers further applied the asymmetric methodology to 2-(alkyloxy)acetaldehydes by employing a cinchona alkaloid-derived co-catalyst and used this chemistry in a synthesis of gliocladin C (**2**, Figure 1). [19,20]

The polypyrroloindoline alkaloids present a particular synthetic challenge due to the presence of vicinal all-carbon quaternary stereocenters and, therefore, the design of methodology tailored to these molecules is an important area of research. Shortly following Gong's report of the enamine alkylation reaction described above, Kanai, Matsunaga and coworkers also reported a concise synthesis of (+)-folicanthine (**35**) (Scheme 6).[21] In this case, installation of the quaternary stereocenters was accomplished by sequential Mn-catalyzed Michael additions of readily available bisoxindole **36** to nitroethylene. Although this transformation proved more practical in terms of yield as a two-step process, it is impressive that the one-flask double Michael addition proceeds with exceptional enantioselectivity to successfully generate both stereocenters in a single step.

Asymmetric nucleophilic catalysis has also been employed in the synthesis of enantioenriched pyrroloindolines. In their synthesis of (+)-gliocladine C (**45**), Overman and coworkers recognized the utility of the planar-chiral ferrocenyl pyridine (**40**)-catalyzed intramolecular acyl O-to-C migration of indolyl carbonates initially disclosed by Fu and Hills.[22,23] Subjection of indolyl trichloro-*tert*-butylcarbonate **39** to the reported migration conditions provided oxindole **41** in high yield and ee (Scheme 7). Following further elaboration, intermolecular aldol reaction of **42** with trioxopiperazine **43** and subsequent exposure to BF_3•OEt_2 provided didehydro-pyrroloindoline **44**. This cyclization product was converted to (+)-gliocladine C (**45**) in 6 steps,[24] representing the first total synthesis of an epidithiodiketopiperazine (ETP) natural product incorporating a β-hydroxy-substituted stereocenter.

As a complementary approach to asymmetric oxindole syntheses described above, Larionov and coworkers reported a strategy that invokes instead the intermediacy of an indolyl 1,2-oxazine (**48**, Scheme 8).[25,26] Similar to the oxindole research, these studies were driven by both the biological activity of 1,2-oxazine natural products[27] and the prospective conversion to pyrroloindolines. Specifically, Lewis acid-catalyzed [4+2] cycloaddition reactions of 3-alkylindoles (**46**) with nitrosoalkenes generated in situ from 2-chlorooximes (**47**) were found to afford the desired oxazines. Notably, Gilchrist and Roberts reported a related non-asymmetric $NaHCO_3$-promoted reaction in 1978,[28] but this recent addition to the literature represents the first catalytic and highly enantioselective cycloaddition of nitrosoalkenes for any dienophile.[29] Beckmann rearrangement of 1,2-oxazine **48** furnished 3-

allylpyrroloindoline **49**, thereby illustrating the utility of this strategy for the synthesis of both oxazines and pyrroloindolines.

Direct Synthesis of Pyrroloindolines from Indoles and Tryptamines

Over the past decade, direct asymmetric functionalization of 3-substituted indoles has emerged as a powerful approach for the efficient preparation of pyrroloindolines. In 2004, MacMillan and coworkers reported a chiral imidazolidinone salt (**52**)- catalyzed reaction between acrolein and tryptamine derivatives (**50**) to generate enantioenriched pyrroloindolines (**51**, Scheme 9).[30] The proposed mechanism invokes condensation of **52** with acrolein to generate a chiral iminium ion,[31] which undergoes a cascade conjugate addition/cyclization reaction to deliver the pyrroloindoline framework. The appeal of this reaction is that it harnesses the intrinsic C3-nucleophilicity of indoles and provides direct access to pyrroloindolines from simple, readily available materials. More recently, the MacMillan group developed organocatalytic cascade reactions of 2-vinyl-tryptamines (**53**) to execute remarkably concise total syntheses of several alkaloids, including minfiensine (**4**, Figure 1).[32]

Since the initial disclosure by MacMillan and coworkers, several other methods for the direct synthesis of pyrroloindolines from tryptamine derivatives have been reported, and collectively these reactions provide access to a variety of enantioenriched pyrroloindoline products. In 2006, Trost and Quancard reported an AAA reaction of tryptamines (**56**) using allyl alcohol, activated by a trialkylborane, as the electrophile (Scheme 10).[33] Notably, the enantioselectivity of this AAA reaction is dependent on the choice of both ligand and borane, with the combination of 9-BBN-C_6H_{13} and anthracene-derived phosphine (*S*,*S*)-**57** proving optimal.[34]

Antilla and Zhang recently reported chiral phosphoric acid (**65**)-catalyzed C–N and C–C bond formation/cyclization reactions of tryptamine carbamates (**59** and **60**) (Scheme 11).[35a] Preliminary NMR investigations suggest a mechanism involving electrophile activation by a hydrogen-bonding network. Specifically, it is proposed that coordination of the tryptamine carbonyl to the catalyst enhances the carbamate acidity and results in hydrogen bonding to the electrophile (either diethylazodicarboxylate (DEAD, see complex **61**) or methyl vinylketone). This methodology constitutes the first catalytic, asymmetric construction of 3-aminopyrroloindolines, a motif present in several naturally occurring alkaloids.[36] Furthermore, the utility of the C-C bond forming variant has been demonstrated in the concise total synthesis of (−)-debromoflustramine B (**64**). Exposure of (1*H*)-tryptamine **60** to methyl vinyl ketone resulted in substitution at both C3a and N1a to give **63**, an intermediate primed for elaboration to **64**. A publication from You and coworkers describing similar findings with a related phosphoric acid catalyst was reported in close timing with the Antilla report (not shown).[35b]

In a recent effort directed toward preparing 3a-arylpyrroloindolines, MacMillan and Zhu developed a Cu(I)- bisoxazoline (**68**)-catalyzed intermolecular arylation of indole carboxamides using aryliodonium salts (**67**, Scheme 12).[37] The proposed mechanism involves C3-metalation of the indole (**66**) by a Cu(III)-aryl complex, reductive elimination, and cyclization of the resultant 3-arylindolenine (**71**). The excellent enantioinduction likely results from bidentate substrate coordination (**70**). This reaction enables the direct preparation of highly enantioenriched pyrroloindolines (**69**) and tolerates a variety of substitution patterns on the arene and indole backbone.

Although the vast majority of direct asymmetric approaches to pyrroloindolines employ tryptamine derivatives as substrates, Reisman and coworkers pursued an alternative strategy involving an (*R*)-BINOL•$SnCl_4$-catalyzed formal (3 + 2) cycloaddition reaction between C3-

substituted indoles (**72**) and benzyl-2- trifluoroacetamidoacrylate (**73**, Scheme 13).[38] This step-wise reaction is proposed to occur by conjugate addition to **73** at C3 of the indole (**72**), followed by protonation of the resultant enolate (**74**) and cyclization to afford the pyrroloindoline (**75**). Mechanistic studies suggest that the enantioselectivity originates from a catalyst-controlled protonation.[39] Although the reaction is sensitive to the steric profile of the indole nucleophile, alkyl substituents are well tolerated, thus providing rapid access to pyrroloindolines including aza-propellane **78**, which contains the core of minfiensine-type alkaloids (**4**, Figure 1), and 5-methoxypyrroloindoline **76**, a potential precursor to physostigmine (**1**, Figure 1). Moreover, this formal cycloaddition reaction offers the only direct access to the C2 pyrrolidine stereocenter found in diketopiperazine-containing natural products.

More recently, Spangler and Davies reported a Rh(II)-catalyzed formal (3 + 2) cycloaddition between C3- substituted indoles and 4-aryl-1-sulfonyl-1,2,3-triazoles to give enantioenriched tetrahydropyrrolo[2,3-*b*]indoles (e.g. **81**, Scheme 14).[40] In this reaction, the 4-aryl-1-sulfonyl-1,2,3-triazole serves as a precursor to a Rh-bound carbenoid. The authors speculate that the reaction proceeds through cyclopropanation of the indole C2-C3 bond to give **82**, followed by fragmentation of the cyclopropane and cyclization to form the dihydropyrrole ring. Good yields and excellent enantioselectivities are obtained for a range of substrates.[41]

With the exception of the formal cycloaddition reaction developed by Reisman and coworkers,[38] the approaches described in this section all rely on setting the absolute stereochemistry of the pyrroloindoline through a key, catalytic, C3-functionalization step. Alternatively, Willis and coworkers pursued a conceptually distinct strategy focused on the desymmetrization of readily accessible *meso*-chimonanthine to prepare the related trispyrroloindoline alkaloid (−)-hodgkinsine B (**86**, Scheme 15).[42] Specifically, a Pd-catalyzed *N*-allylation of bispyrroloindoline **84** was achieved using the ligand (*R*,*R*)-**20**, a chiral phosphine developed by Trost and coworkers (Scheme 3).[43] This chemistry finds precedent in Taguchi and coworkers' Pd-catalyzed desymmetrization of *meso*-cyclohexane-1,2-diamides,[44] but the substrate complexity and enantioselectivity are unparalleled. In combination with the oxindole α-arylation methodology also developed by Willis and coworkers,[45] this allylic substitution-desymmetrization reaction enabled remarkably rapid access to **86**.

The complexity, biological activity, and remarkable variety exhibited by pyrroloindolines have long established this family of natural products as an important target for total synthesis. In particular, the past two decades of research resulted in enantioselective, catalytic strategies for the synthesis of pyrroloindolines bearing C3a all-carbon quaternary stereocenters. Whereas early synthetic methods focused on the preparation of 3,3′-disubstituted oxindoles, more recent efforts have started to explore the direct functionalization of indoles. Despite the breadth of reported transformations, key restrictions exist regarding functional group incorporation and there is no singular method that is best for the preparation of the diverse array of structures found in pyrroloindoline alkaloids. These unmet challenges illustrate the demand for new methodologies and suggest that the pyrroloindoline scaffold will persist as an inspiration for future research in organic synthesis.

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Biographies

Lindsay Repka was born and raised in Baltimore, Maryland. Lindsay earned her B.A. in Chemistry from Barnard College and completed her Ph.D. in 2013 under the direction of Prof. Sarah Reisman at the California Institute of Technology. She will join the group of Prof. Wilfred van der Donk at the University of Illinois at Urbana–Champaign as a postdoctoral researcher in the fall of 2013.

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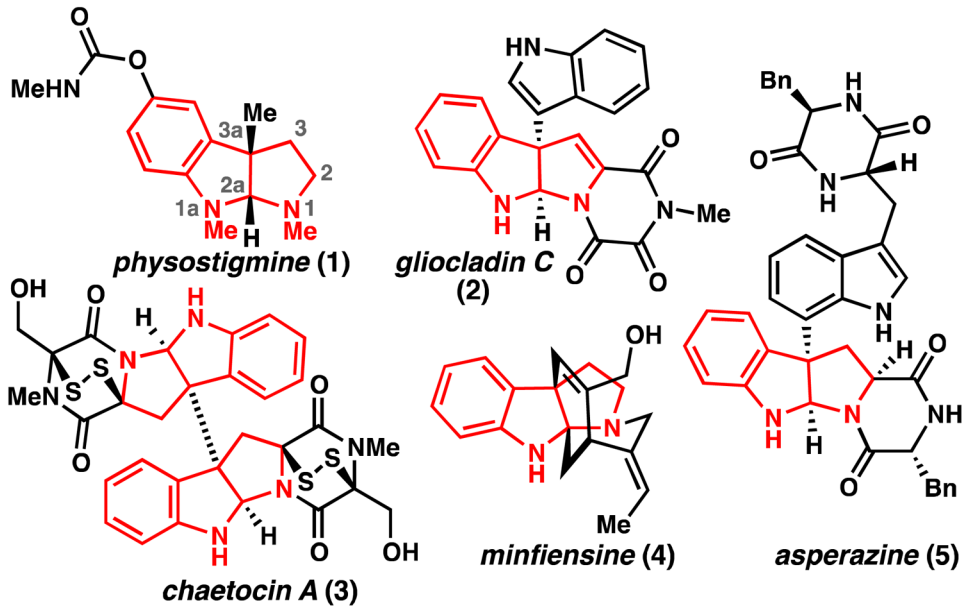
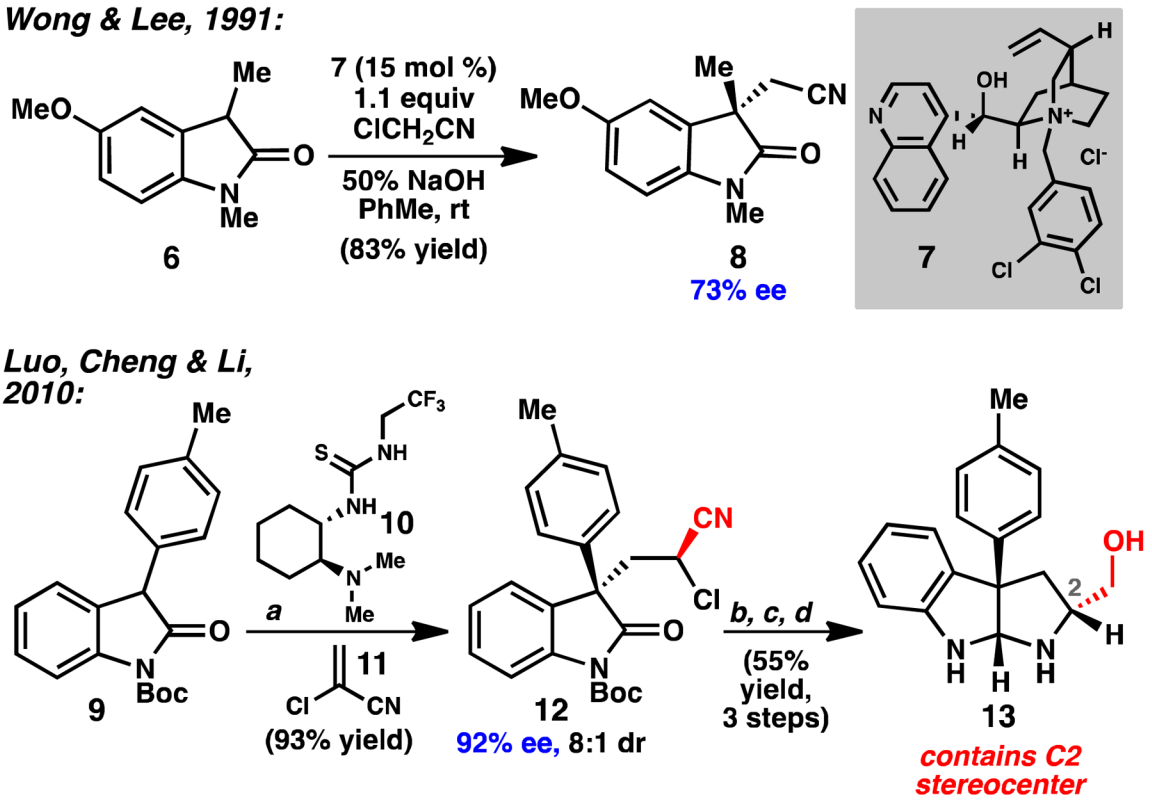


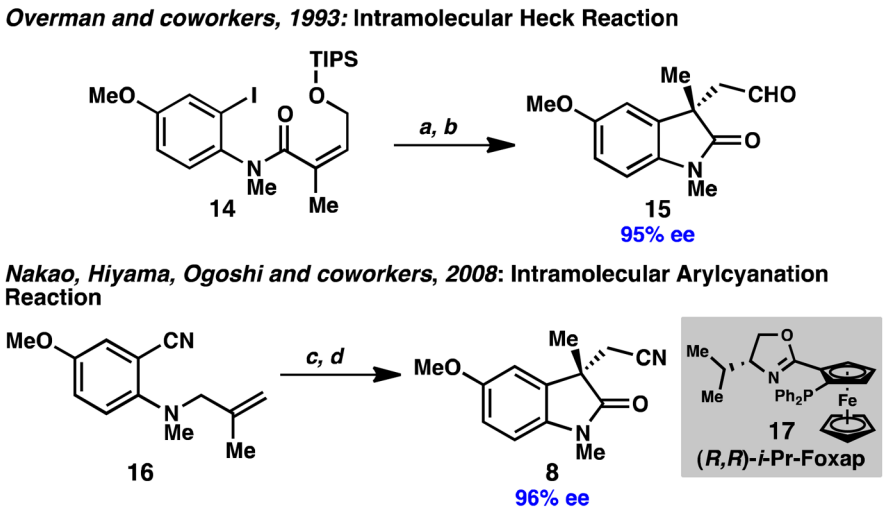
Figure 1.
Representative pyrroloindoline natural products.



Scheme 1.

Organocatalytic α-alkylation of oxindoles.

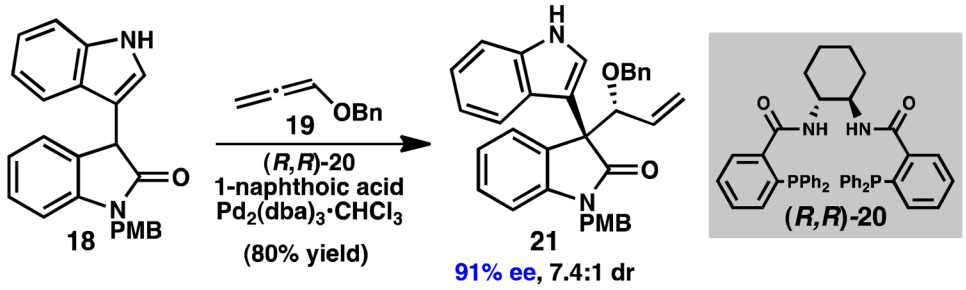
Conditions: (*a*) 3.0 equiv **11**, 10 mol % **10**, 4Å MS, $ClCH_2CH_2Cl$, −20 °C, 48 h; (*b*) NaN_3, DMSO, 30 °C, 24 h; (*c*) TMSCl, MeOH, rt, 96 h; (*d*) Red-Al, PhMe, rt to 100 °C, 24 h.



Scheme 2.

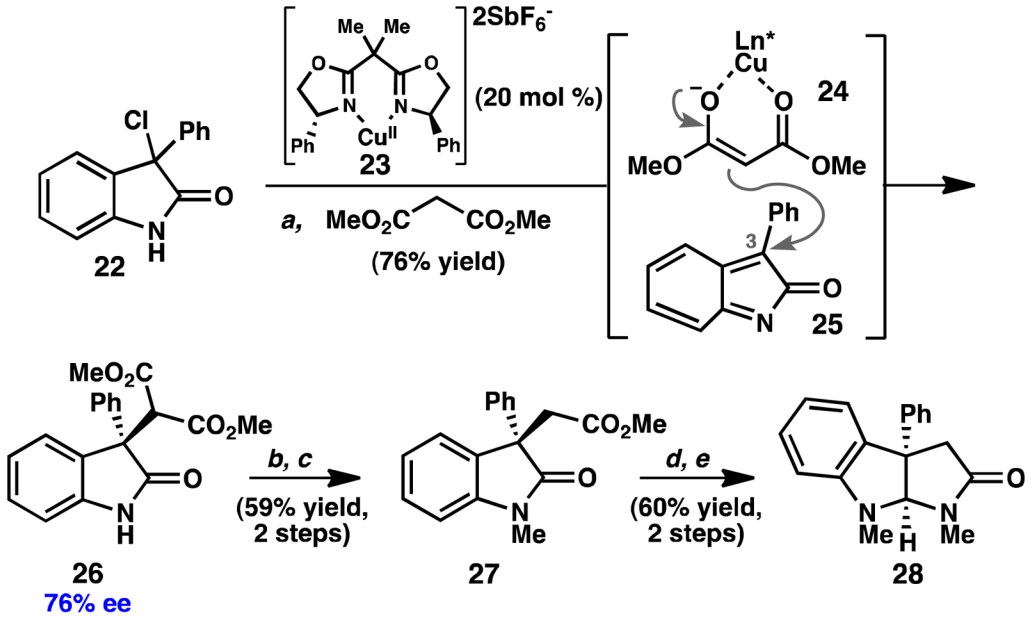
Cyclization approaches to 3,3′-disubstituted oxindoles.

Conditions: (*a*) 10 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 23 mol % (*S*)-BINAP, 5.1 equiv PMP, DMA, 100 °C, 1.5 h. (*b*) 3 *N* HCl, 0 to 23 °C (84 % yield, 2 steps). (*c*) 10 mol % $Ni(cod)_2$, 20 mol % **17**, 40 mol % $AlMe_2Cl$, DME, 100 °C, 10 h (88% yield); (*d*) 6.0 equiv PhIO, CH_2Cl_2, rt, 2.5 h (40% yield).



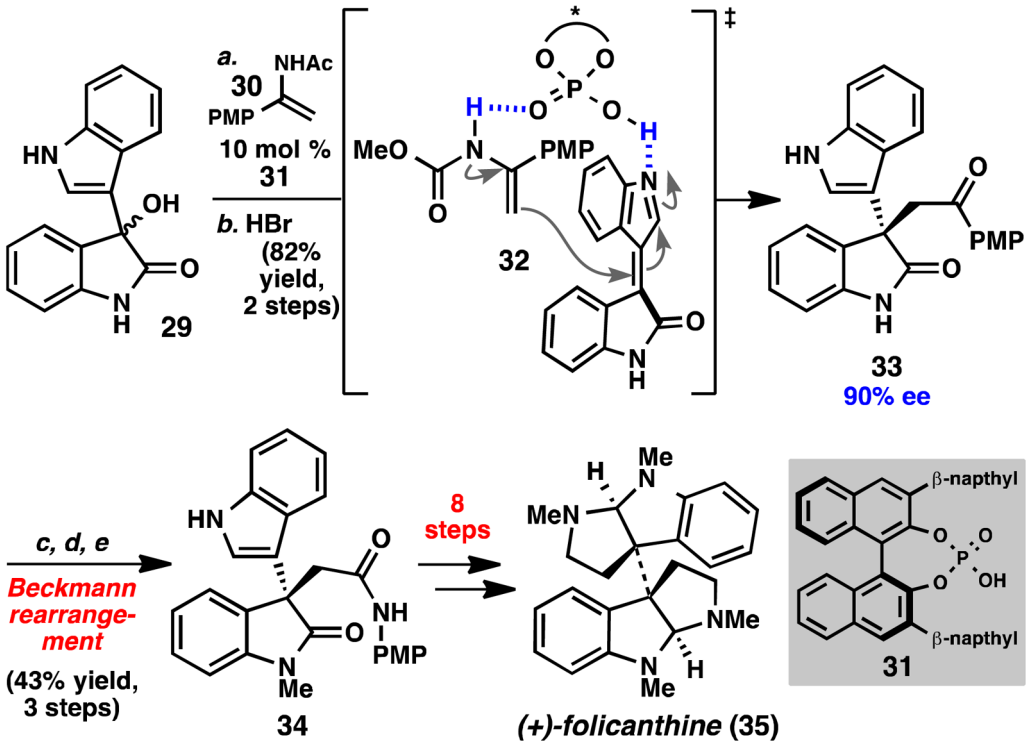
Scheme 3.

Pd-catalyzed allylation of oxindoles with benzyloxyallene (**19**) (Trost and Zhang, 2011). Conditions: 1.2 equiv **19**, 2.5 mol % $Pd_2(dba)_3$•$CHCl_3$, 7.5 mol % (*R*,*R*)-**20**, 5 mol % 1-naphthoic acid, THF, rt, 41 h.



Scheme 4.

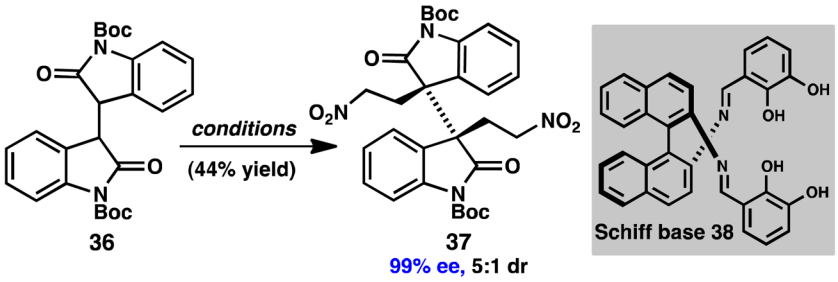
Cu-catalyzed Umpolung alkylation of 3-halooxindoles (Stoltz and coworkers, 2009). Conditions: (*a*) 20 mol % (*S*)-PhBOX·Cu(II)·2SbF_6, 3.0 equiv dimethyl malonate, 2.0 equiv Et_3N, 3 Å MS, CH_2Cl_2, −20 °C (76% yield). (*b*) LiCl, H_2O, DMSO, 150 °C, 12 h; (*c*) *t*BuOK, MeI, THF, 0 °C, 1 h; (*d*) $AlMe_3$, $MeNH_2$•HCl, PhMe, 50 °C, 5 d; (*e*) LAH, THF, 0 °C, 1 h.



Scheme 5.

Phosphoric acid-catalyzed Umpolung alkylation of 3-indolyloxindoles en route to (+)-folicanthine (**35**) (Gong and coworkers, 2012).

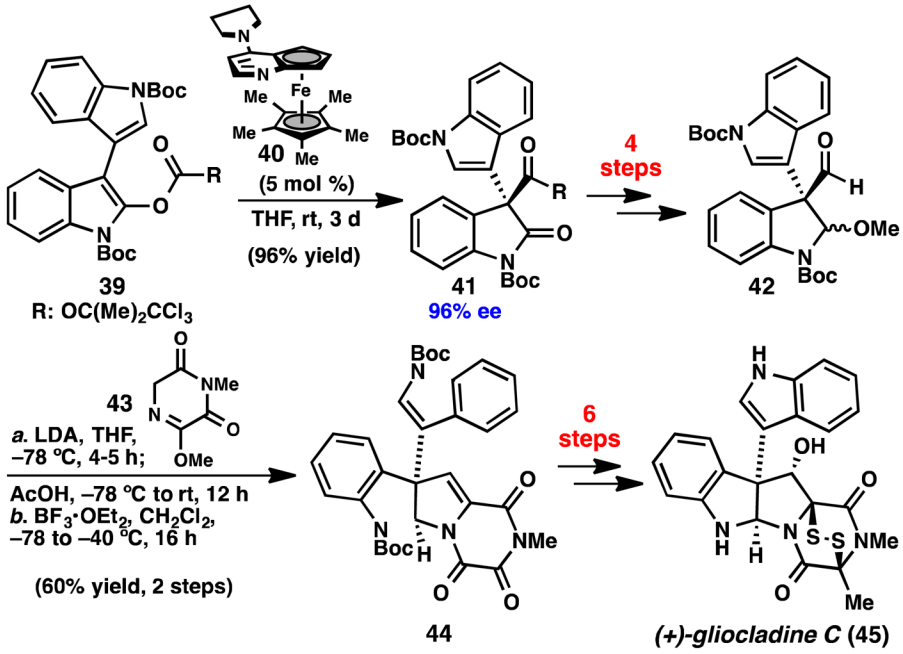
Conditions: (*a*) 1.5 equiv **30**, 10 mol % **31**, Na_2SO_4, CH_2Cl_2, rt, 12–24 h; (*b*) aqueous HBr, EtOH, rt, 8 h; (*c*) nBu_4NHSO_4, KOH, THF, 50 °C, 1 h; then MeI, rt, 2 h; (*d*) NH_2OH•HCl, pyridine, EtOH, rt, 2 d; (*e*) $HgCl_2$, MeCN, 80 °C, 2 h.



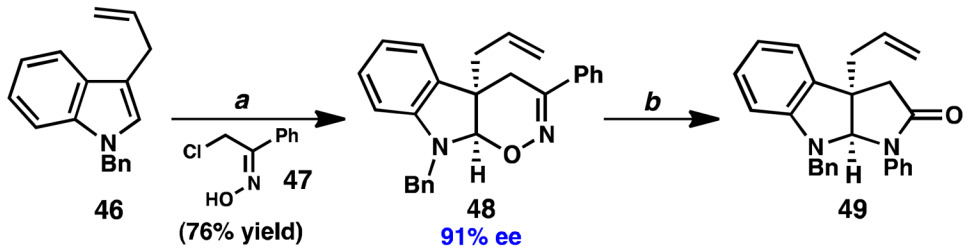
Scheme 6.

Mn-catalyzed double Michael reaction en route to (+)-folicanthine (**35**), (Kanai, Matsunaga and coworkers, 2012).

Conditions: 1.2 equiv nitroethylene, 18 mol % Mn(4-F-BzO)$_2$/**38** (ratio 1:1), PhMe, 5Å MS, 50 °C, 1.5 h; then 2.0 equiv nitroethylene, 1.0 equiv 2,6-di-*tert*-butylphenol, 50 °C, 12 h.



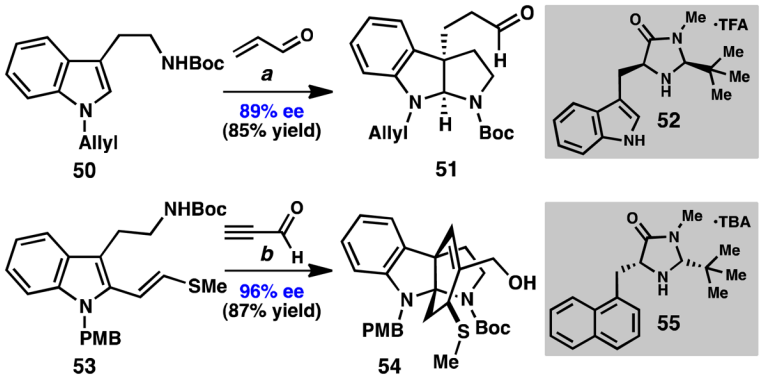
Scheme 7.
First synthesis of a β-hydroxy-ETP natural product (Overman and coworkers, 2011).



Scheme 8.

Nitrosoalkene [4+2]/Beckmann rearrangement approach via a 1,2-oxazine intermediate (Larionov and coworkers, 2012).

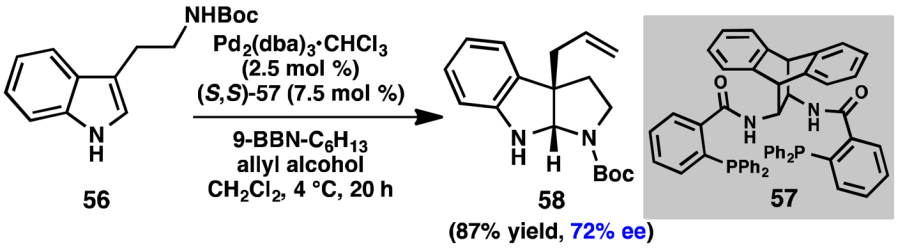
Conditions: (*a*) 10 mol % CuOTf•1/2PhMe, 10 mol % (*S*)-DM-BINAP, 3.0 equiv Ag_2CO_3, 3Å MS, CH_2Cl_2, −15 °C, 48 h; (*b*) 20 mol % PBr_3, $C_6H_5CF_3$, 50 °C, 16 h (79% yield).



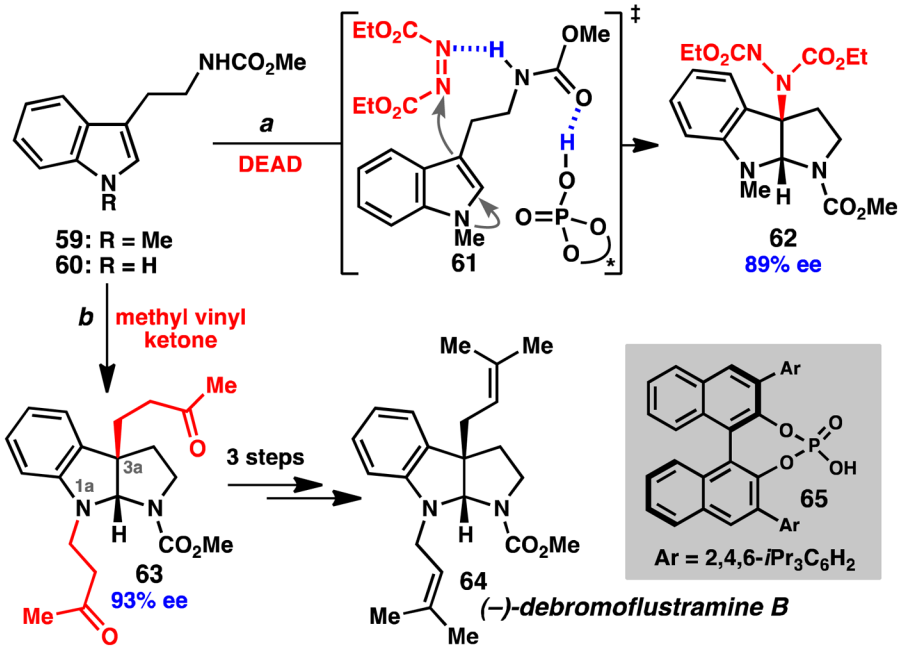
Scheme 9.

First direct, enantioselective construction of pyrroloindolines from tryptamines (MacMillan and coworkers, 2004 and 2009).

Conditions: (*a*) Acrolein (4.0 equiv), **52** (20 mol %), 85:15 CH_2Cl_2:H_2O, −85 °C, 25 h. (*b*) Propynal (3.0 equiv), **55** (15 mol %), Et_2O, −40 °C, 24 h; $NaBH_4$, $CeCl_3$, MeOH.



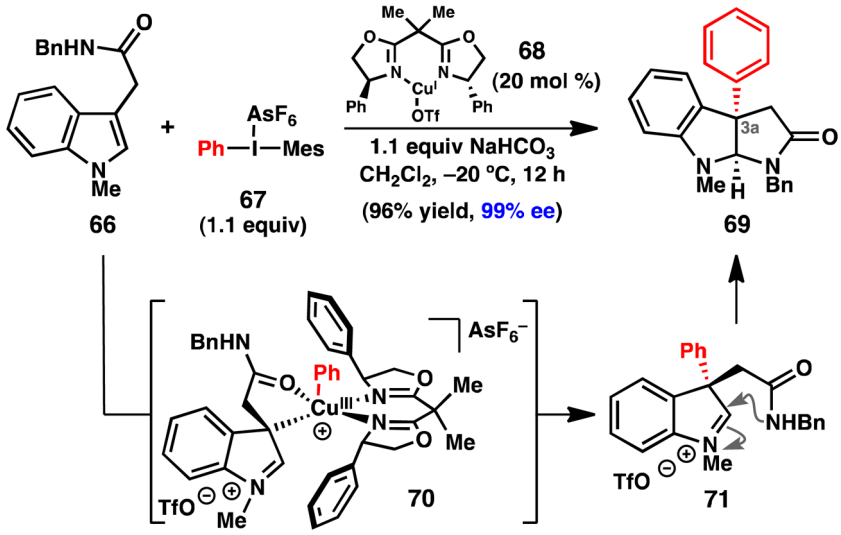
Scheme 10.
Pd-catalyzed tandem allylic alkylation/cyclization reaction of tryptamines (Trost and Quancard, 2006).



Scheme 11.

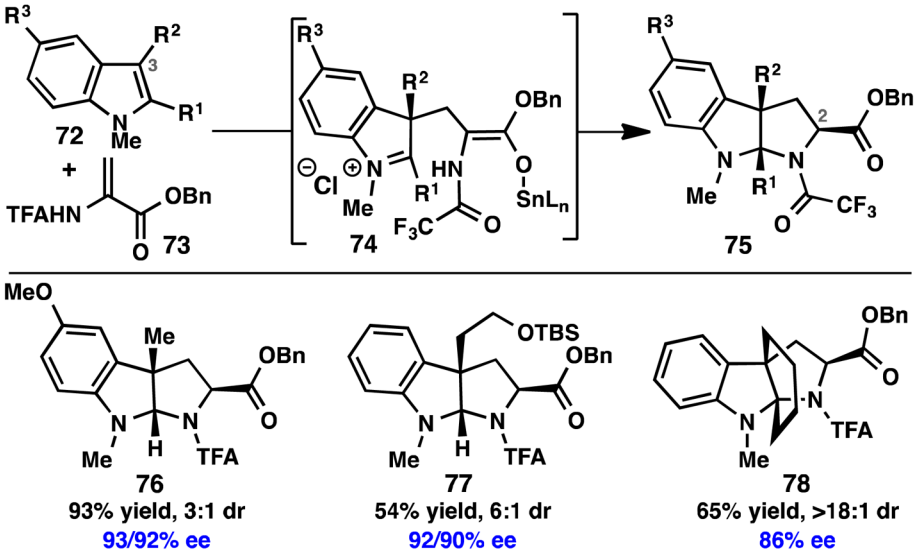
Phosphoric acid (**65**)-catalyzed preparation of two pyrroloindoline motifs (Antilla and Zhang, 2012).

Conditions: (a) DEAD (1.5 equiv), **65** (10 mol %), PhMe, 50 °C, 48 h (76% yield). (b) Methyl vinyl ketone (3.0 equiv), **65** (10 mol%), 4 Å MS, 1:1 PhMe:PhH, −20 °C, 24 h (91% yield).



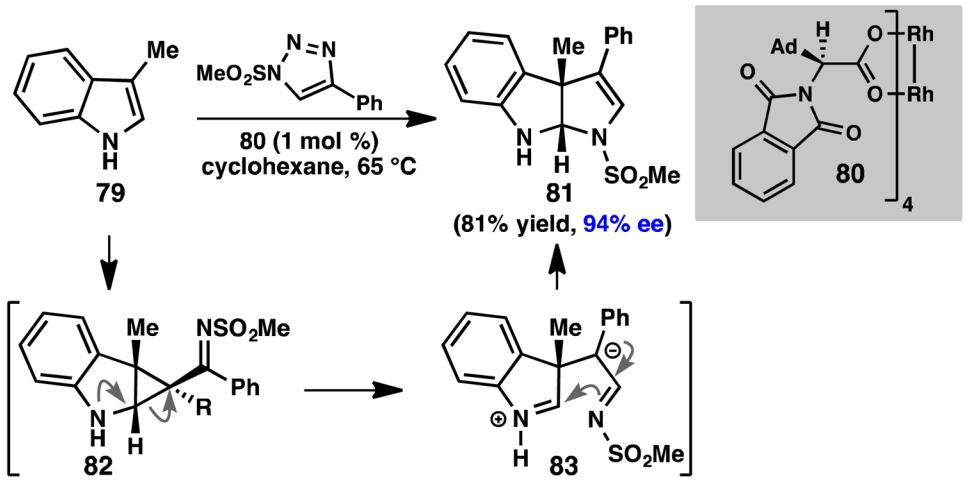
Scheme 12.

Cu-catalyzed tandem arylation/cyclization reaction of indole carboxamides (MacMillan and Zhu, 2012).

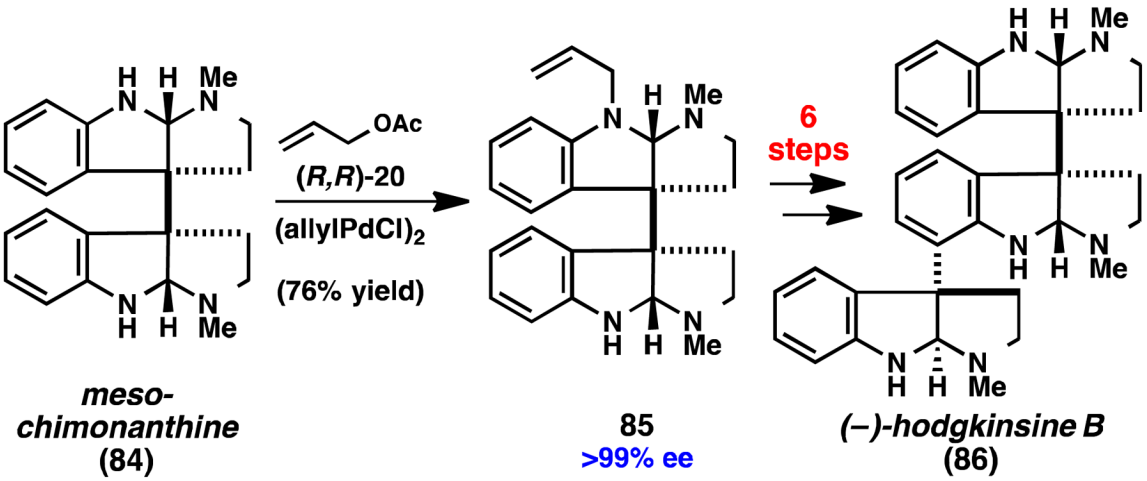


Scheme 13.

(*R*)-BINOL• $SnCl_4$-catalyzed formal cycloaddition reaction (Reisman and coworkers, 2010). Conditions: 1.2 equiv $SnCl_4$, 20 mol % (*R*)-BINOL, CH_2Cl_2, 23 °C, 4–20 h.



Scheme 14.
Rh(II)-catalyzed asymmetric annulation of indoles (Spangler and Davies, 2013).



Scheme 15.

Allylic substitution-desymmetrization reaction en route to (−)-hodgkinsine B (**86**) (Willis and coworkers, 2011).

Conditions: 1.2 equiv allyl acetate, 2.0 equiv Et_3N, 3.8 mol % (*R*,*R*)-**20**, $(allylPdCl)_2$ (1.25 mol %), PhMe, 0 °C, 1.5 h.